REMARKS

Claims 1-53 are pending in this application. Claims 29-53 were previously withdrawn, but are herewith amended, as discussed below (*see* ¶1 below). Claims 1, 4, 6, 7, 16, 18-20, 29 and 40-41 are amended. Support for the amendments to these claims can be found, for example, in previous claims 1, 4, 6-7, 11-13, 16, 18-20, 22, 24-26, 29 and 40-41 and in the specification. Specifically, support for "buffered saline" can be found, for example, on pg. 3, lines 24-28; pg. 4, lines 15-16; pg. 7, lns. 18-21; pg. 14, lines 3-11 and 13-15; and pg. 21, Table 1. Support for the phrase "for therapeutic use in humans" and the inclusion of the formulation of claims 1 or 16 in amended claim 29 can be found, for example, on pg. 15, ln. 8 to pg. 17, ln. 5; pg. 18, ln. 9 to pg. 19, ln. 30; and pg. 25, ln. 7 to pg. 29, ln. 28. Support for the phrase "'a therapeutic concentration of' botulinum toxin" can be found in claims 9, 11-13, 22, 24-26, and in the specification on pg. 13, lns. 20-27; pg. 17, ln. 6 to pg. 20, ln. 1; pg. 24, ln. 6 to pg. 29, ln. 28. In the interest of expediting prosecution of this application, Applicants have removed the term "$\pm$ 10%" from claims 1, 4, 16 and 18 in regards to the range of the recited pH. Applicants reserve the right to include these broader ranges in one or more co-pending applications. Applicants have also amended therapeutic method claims 29-53 to include the stabilized liquid pharmaceutical botulinum toxin formulations of claims 1 or 16, as indicated by the Examiner Interview of September 7, 2005 (*see* discussion at ¶1 below).

Claims 1-53 are therefore now pending in the present application. Reconsideration and allowance of this application is respectfully requested in view of the following remarks.

I. Interview Summary

Applicants thank the Examiner for the courtesy extended to Applicants in granting the interview on September 7, 2005 regarding the general nature of the invention and the Office Action, dated July 21, 2005. Applicants discussed proposed amendments made in response to the 35 U.S.C. § 112 rejection. Applicants also discussed the limitations regarding pH and the range encompassed by the term "$\pm$ 10%." In addition, Applicants discussed the state of the art in terms of purification of botulinum toxin, and the term "pharmaceutical" in regards to the limitation "purified botulinum toxin," and the limitation "buffered saline." Applicants also discussed the status of the European

Opposition proceedings. Applicants offered to provide the latest filings in the Opposition proceedings, which have been sent in a separately filed Information Disclosure Statement, dated September 9, 2005. Finally, in the interest of efficiently consolidating the prosecution of the instant application, Applicants discussed the pursuance of previously withdrawn method claims 29-53. The Examiner indicated willingness to consider pursuance of the therapeutic method claims if the previously withdrawn claims were amended accordingly to include the formulation of claims 1 and 16.

II. Withdrawn Claim Rejections

The Examiner has stated that the 35 U.S.C. § 102(b) rejection of claims 16, 17, 21 and 27, and the 35 U.S.C. § 112 rejections of claim 1-28 have been withdrawn. Applicants wish to thank the Examiner for this action, and duly note that the §§ 102(b) and 112 rejections have been withdrawn.

III. Claim Rejection Under 35 U.S.C. 112, Second Paragraph:

The Examiner rejected claims 6, 7, 19 and 20 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Applicants have amended dependent claims 6, 7, 19 and 20 to replace the term "buffer" with "buffered saline."

Based on these amendments and the comments above, Applicants respectfully request withdrawal of this rejection.

IV. Claim Interpretation by the Examiner

The Examiner has stated that that the limitation "purified" botulinum toxin is interpreted as not limited to "fully purified" botulinum toxin, but encompasses a botulinum toxin of any degree of purity. *See* Office Action at ¶10. The Examiner has also stated that "the limitation 'said buffer' in the dependent claims 6, 7, 19 and 20 and the limitation 'buffered saline' in the independent claims 1

and 16 are viewed as having the same scope." *See id.* Applicants respectfully disagree with the Examiner on these claim interpretations.

Interpretation of the Term "Purified"

Applicants respectfully disagree with the Examiner in regards to the interpretation of the term "purified." First, Applicants respectfully point out that pending claim 1 recites a "pharmaceutical" botulinum toxin formulation for "therapeutic use in humans", *i.e.*, a botulinum toxin preparation that is safe for therapeutic use in humans using methods employed by those of ordinary skill in the art. *See, e.g.*, pg. 8, lines 1-2 for definition of "pharmaceutically acceptable liquid." Second, Applicants give ample examples in the specification regarding the process necessary for obtaining purified botulinum toxin, including column chromatography purification of ammonium sulfate precipitated preparations. *See* especially pg. 12, line 5 ("This *purified* toxin preparation can be used to prepare the formulation.") (emphasis added). Therefore, a botulinum toxin cannot be of "any degree of purity", as alleged by the Examiner. The toxin preparation should be free of the majority of impurities and contaminants that are present in non-column chromatographed preparations.

Moreover, as mentioned above, the toxin preparation should be safe for consumption, *i.e.* it cannot be harmful or lethal when administered for "therapeutic use in humans". The specification provides ample guidance to one of ordinary skill in the art in terms of safety of the botulinum toxin preparation. For example, the specification defines the term "pharmaceutically acceptable liquid" as a liquid which is "considered to be safe for consumption or by injection into mammals, particularly humans." *See* specification at pg. 8, lines 1-2. A preparation that is harmful or lethal, *e.g.* of extremely high concentrations, yet is of sufficient purity still cannot be considered to be "safe for consumption or by injection" into humans. In other words, even if sufficiently pure, harmful or lethal concentrations of botulinum toxin preparations would not be considered to be a "pharmaceutical" preparation. Understandably, a "liquid ***pharmaceutical*** botulinum toxin formulation for ***therapeutic*** use in humans" must meet these requirements in order to be administered into human patients, as is demonstrated in the present application.

Applicants respectfully requests the Examiner to reconsider the claim interpretation stated in light of the above arguments.

Interpretation of the Term "Buffered Saline" and "Buffer"

As a preliminary remark, Applicants wish to thank the Examiner for taking the time to explain her interpretation of the term "buffered saline" during the interview. Applicants have considered and studied the Examiner's comments carefully. Applicants respectfully submit that although the terms "buffered saline" and "buffer" perform the same function of buffering, they nonetheless do not have the same scope or meaning as put forth by the Examiner because "buffered saline" further defines the term "buffer" suitable for use in this invention in requiring the presence of a saline component.

Applicants first point out from a plain language interpretation of the terms that although the terms do have "buffer" as a commonality, they differ in one aspect: the presence (or absence) of the term saline. *See* MPEP §2111. The term "buffer" is defined as a compound "that serves to maintain the free hydrogen ion concentration of the solution within a certain pH range, when hydrogen ions are added or removed from the solution." *See* pg. 7, lines, 23-25. Saline solutions, as understood by one of ordinary skill in the art, in contrast, cannot by itself maintain "the free hydrogen ion concentration of a solution", especially when hydrogen ions are added or removed from the solution. Instead, buffer compounds are needed in order to accomplish this task, and are in fact added to a saline solution to provide this function. Buffered saline solutions, therefore, even though performing the same function through the common addition of a buffer, are not of the same composition as a "buffer" because they possess the extra limitation of saline.

Federal Circuit precedent supports Applicant's interpretation of the term "buffered saline" and the need to interpret terms in their context. The Federal Circuit has consistently ruled that words of a claim should be "generally given their ordinary and customary meaning" when construing the terms of a claim. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005); quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). In *Phillips*, the Federal Circuit gave guidance as to the importance of context when determining the ordinary and customary meaning of a claim term. *Phillips,* 415 F.3d at 1313-1314. The Court, in construing the claim term

"steel baffles" noted that the ***context*** of this term within the claim was highly instructive to one of ordinary skill in the art when interpreting claim language:

> To take a simple example, the claim in this case refers to "steel baffles," which strongly implies that the term "baffles" does not inherently mean objects made of steel.

Id. at 1314. Thus, the Court emphasized the importance of context during claim interpretation by concluding that two words, when placed side-by-side, cannot be of the same meaning or same scope. The Court has in numerous instances emphasized the use of a term within a claim as a firm basis for interpreting claim language. *See, e.g., Mars, Inc. v. H.J. Heinz Co.,* 377 F.3d 1369 (Fed. Cir.2004); *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1356 (Fed. Cir. 1999).

As in *Phillips*, where the Federal Circuit noted that the term "steel baffles" cannot mean that baffles are inherently made of steel, the same conclusion can be drawn where the term "buffered saline" strongly implies that "saline" compositions are not inherently "buffered," or the converse that all "buffered" solutions do not inherently contain "saline." In other words, the term "buffered" is, and should be treated separately from the term "saline."

In addition, Applicants also respectfully submit that one of ordinary skill in the art at the time of filing of the instant application would be familiar with the definition of "saline," as an isotonic solution of sodium chloride, usually 0.9%, used readily in pharmaceutical formulations. *See, e.g.*, United States Pharmacopeia (USP) 23, National Formulary (NF) 18, at pg. 2056, defining saline as 0.9% sodium chloride solution; attached herein. One of ordinary skill in the art would also know that for a formulation or solution to be adequately "buffered," an appropriate "buffer" must be added. *See* L. Lachman *et al.*, in THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY, 3rd ed. (1986), pgs. 459-460 (cited in specification; already of record). The specification provides adequate support in the Examples, where an exemplary embodiment of a stable botulinum toxin formulation contains both a buffer compound (succinate) and sodium chloride (100 mM) at an amount sufficient (approximately 0.6% NaCl) to raise the tonicity of the formulation, taking into account the tonicity contribution of the succinate buffer compound, botulinum toxin and albumin components, for appropriate "therapeutic use in humans." *See* Table I at pg. 21. Therefore, one of ordinary skill in

the art, with guidance from the specification and dependent claims as mentioned above, would know that "buffered saline" and "buffer" do not have the same scope or meaning.

Applicants respectfully submit that the claim interpretations put forth by the Examiner should be reconsidered in light of the above comments.

V. Rejections Under 35 U.S.C. § 102

A. The Schwarz Reference Does Not Anticipate the Instant Claims Because it Does Not Disclose a "Buffered Saline" or a "Pharmaceutical Botulinum Toxin Formulation" at "A Therapeutic Concentration"

The Examiner rejected claims 1-8 and 16-21 under 35 U.S.C. 102(b) as allegedly anticipated by Schwarz *et al.* (Archiv. fur Lebensmittelhygiene 30: 1-40, pp. 29-33 (1979)). Applicants respectfully traverse this rejection.

The Examiner states that Schwarz teaches a "stable liquid pharmaceutical formulation comprising a purified serotype B botulinum toxin and an acetate buffer solution having a pH in the range of 4.5 to 5.6, or a phosphate buffer at a pH of 6.0." *See* Office Action at ¶11. Applicants first note that the Schwarz article does not disclose the use of a "stable liquid pharmaceutical botulinum toxin formulation comprising a pharmaceutically acceptable buffered ***saline***." *See* claims 1 and 16 of the instant specification. Instead, the Schwarz article discloses crude and DEAE purified toxin in 0.05 M either acetate or phosphate buffer in the absence of a saline environment. *See, e.g.*, Schwarz article pg. 3, 1st and 3rd full paragraphs. As the Examiner knows, "[a] claim is anticipated only if each and every element as set forth in the claim is found." MPEP § 2131. As argued above, and as what one of ordinary skill in the art would understand, acetate or phosphate buffer does not equate to a "buffered saline." Because the Schwarz article does not disclose a buffered saline, it cannot anticipate the instant claims.

In addition, Applicants respectfully point out to the Examiner that the Schwarz article discloses highly concentrated formulations of botulinum toxin that would not be considered by one of ordinary skill in the art to be a "liquid ***pharmaceutical*** botulinum toxin formulation" at "a ***therapeutic concentration*** suitable for use in humans of purified botulinum toxin" for "***therapeutic***

use in humans." *See* amended claims 1 and 16. As stated in the Schwarz article, pH adjustment was done via a Sephadex G25s column, not through dilution of the crude and column-chromatography purified toxin preparations. *See* pg. 3, 1st full paragraph. Therefore, the botulinum toxin would be at a highly concentrated, and highly lethal, state. This formulation would not be considered to be a ***pharmaceutical*** formulation, nor would it be considered to be ***therapeutically*** useful precisely because of its extreme lethality, and instead would be considered to be a stock solution from which pharmaceutical formulations are made. *See, e.g.*, instant specification at pg. 13, ln. 20-25; Schantz *et al.*, EP 0 593 176 at pg. 3, lines 22-24 (already of record).

The specification gives sufficient guidance and teaching to one of ordinary skill in the art to the contents of a "liquid pharmaceutical botulinum toxin formulation," in regards to excluding concentrated toxin formulations eluted from a purification column chromatography column, as is the case for the Schwarz reference. For example, the specification defines the term "pharmaceutically acceptable liquid" as a liquid which is "considered to be safe for consumption by or injection into mammals, particularly humans." *See* specification at pg. 8, lines 1-2. Although the specification allows for a concentrated solution formulation "which is diluted in a similar or different liquid prior to use," *see* pg. 7, lines 21-22, the magnitude of dilution needed for the Schwarz botulinum toxin preparation is so large that it would be unmanageable and dangerous for one of ordinary skill in the art to prepare or dilute this lethal formulation to a ***pharmaceutical*** formulation "prior to use." Applicants respectfully submit that the Schwarz formulation is not a "liquid pharmaceutical botulinum toxin formulation," and therefore does not anticipate the instant claims.

In light of the arguments above, Applicants respectfully request that the Examiner withdraw this rejection.

B. The Saprykina Reference Does Not Anticipate the Instant Claims Because It Does Not Disclose a "Buffered Saline" or a "Pharmaceutical Botulinum Toxin Formulation" at "A Therapeutic Concentration"

The Examiner rejected claims 1-8 and 16-21 under 35 U.S.C. 102(b) as allegedly anticipated by Saprykina *et al.* (Zh. Mikrobiol. Epidemiol. Immunobiol. 9:86-91, 1980). Applicants respectfully traverse this rejection.

The Examiner states that Saprykina disclosed a liquid botulinum type B toxin formulation comprising acid-precipitated toxin which was subsequently extracted with citrate-phosphate buffer with a pH of 5.6. Applicants first note that the Saprykina article does not disclose the use of a "stable liquid pharmaceutical botulinum toxin formulation comprising a pharmaceutically acceptable buffered ***saline***." *See* claims 1 and 16 of the instant specification. Instead, the Saprykina article discloses crude purified toxin in citrate-phosphate buffer at pH 5.6 in the absence of a saline environment. *See, e.g.*, pg. 4, 3rd full paragraph. As the Examiner knows, "[a] claim is anticipated only if each and every element as set forth in the claim is found." MPEP § 2131. As argued above, and as what one of ordinary skill in the art would understand, citrate- phosphate buffer does not equate to a "buffered saline." There is no saline component in the buffers disclosed in Saprykina. Therefore, because the Saprykina article does not disclose a buffered saline, it cannot anticipate the instant claims.

In addition, Applicants respectfully point out to the Examiner that the Saprykina article discloses highly concentrated formulations of botulinum toxin that would not be considered by one of ordinary skill in the art to be a liquid ***pharmaceutical*** botulinum toxin formulation" at "a ***therapeutic concentration*** of purified botulinum toxin" for "***therapeutic use*** in humans." *See* amended claims 1 and 16. The Saprykina article performed hydrochloric acid precipitations of bacterial cell culture media, and dissolved the precipitations in a pH 5.6 buffer for subsequent loading onto a DEAE cellulose column at an amount equivalent to "20 to 500 mg" of toxin. *See* pg. 5, 1st full paragraph (translated version). At these amounts, the botulinum toxin formulation would be at a highly concentrated, and highly lethal, state. This formulation would not be considered to be a ***pharmaceutical*** formulation, nor at a ***therapeutic concentration*** precisely because of its extreme

lethality, and instead would be considered a stock solution from which pharmaceutical formulations are made. *See, e.g.*, instant specification at pg. 13, ln. 20-25; Schantz *et al.*, EP 0 593 176 at pg. 3, lines 22-24 (already of record).

As was mentioned above, the specification gives sufficient guidance and support to one of ordinary skill in the art in regards to the contents of a "liquid pharmaceutical botulinum toxin formulation" at "a therapeutic concentration" to be excluding concentrated toxin formulations eluted from a purification column chromatography column, as is the case for the Saprykina reference. Applicants respectfully submit that the Saprykina formulation is not a "liquid pharmaceutical botulinum toxin formulation," and therefore does not anticipate the instant claims.

In light of the arguments above, Applicants respectfully request that the Examiner withdraw this rejection.

C. The Sacks Reference Does Not Anticipate the Instant Claims Because It Does Not Disclose A "Buffered Saline" or a "Pharmaceutical Botulinum Toxin Formulation"

The Examiner rejected claims 1-8 and 16-21 under 35 U.S.C. 102(b) as allegedly anticipated by Sacks *et al.* (Applied Microbiology 28:374-382, 1974). Applicants respectfully traverse this rejection.

The Examiner alleges that Sacks disclosed a botulinum toxin formulation in a pH 6.0 phosphate buffer. *See* Office Action at ¶13. The Examiner also alleges that Sacks *et al.* discloses a preparation of a purified *Clostridium botulinum* type E toxin contained in a pH 4.5 buffer which allegedly retained significant toxic activity. *See id.* Applicants first respectfully point out to the Examiner that a pH of 4.5 is not within the "between pH 5 and 6" limitation of the amended claims. Therefore, the pH 4.5 formulation does not anticipate the instant claims because it is outside the scope of the claims.

Applicants also disagree with the Examiner's assessment that the pH 6.0 botulinum toxin E preparation disclosed in the Sacks *et al.* reference was "stable." Sacks *et al.* notes that the liquid formulation stored in pH 6.0 phosphate buffer for 1 year at 4.0 °C "lost more than 60% of its original lethality." One of ordinary skill in the art, with guidance from the specification, would know that a

loss of 60% of the original lethality is not a stable formulation. In fact, this amount is equivalent to the large losses found in prior art formulations, where losses of 44% and 70% of potency were reported in reconstituted botulinum toxin A formulations. *See* pg. 2-3 of the application. Therefore, one of ordinary skill in the art would not consider this formulation to be "stable." In contrast, the instant amended claims require that the stabilized liquid botulinum toxin formulation be "capable of being stable when stored" at the recited temperature and time limitations. The Sacks reference does not disclose a stabilized liquid botulinum toxin formulation that meets these requirements.

In addition, Applicants note that the Sacks reference does not disclose the use of a "liquid pharmaceutical botulinum toxin formulation comprising a pharmaceutically acceptable buffered ***saline***." *See* claims 1 and 16 of the instant specification. Instead, the Sacks article discloses botulinum toxin in the absence of a saline environment. *See, e.g.*, pg. 4, 3rd full paragraph. As the Examiner knows, "[a] claim is anticipated only if each and every element as set forth in the claim is found." MPEP § 2131. As argued above, and as what one of ordinary skill in the art would understand, phosphate buffer does not equate to a "buffered saline." Because the Sacks article does not disclose a buffered saline, it cannot anticipate the instant claims.

In addition, for the same reasons mentioned above, Applicants respectfully point out to the Examiner that the Sacks article discloses highly concentrated formulations of botulinum toxin that would not be considered by one of ordinary skill in the art to be a "liquid ***pharmaceutical*** botulinum toxin formulation" at "a ***therapeutic concentration*** suitable for use in humans of purified botulinum toxin." *See* amended claims 1 and 16. The formulations disclosed in the Sacks reference would not be considered to be a ***pharmaceutical*** formulation, nor is it at "a ***therapeutic concentration*** suitable for use in humans of purified botulinum toxin" precisely because of its extreme lethality, and instead would be considered to be a stock solution from which pharmaceutical formulations are made. *See, e.g.,* instant specification, pg. 13, lns. 20-25; Schantz *et al.*, EP 0 593 176 at pg. 3, lines 22-24 (already of record).

As was mentioned above, the specification gives sufficient guidance and teaching to one of ordinary skill in the art in regards to the contents of a "liquid pharmaceutical botulinum toxin formulation" and "a therapeutic concentration of purified botulinum toxin" to be excluding

concentrated toxin formulations eluted from a purification column chromatography column, as is the case for the Sacks reference. Applicants respectfully submit that the Sacks formulation is not a "liquid pharmaceutical botulinum toxin formulation," and therefore does not anticipate the instant claims.

In light of the arguments above, Applicants respectfully request that the Examiner withdraw this rejection.

D. The Schantz Reference Does Not Anticipate the Instant Claims Because It Does Not Disclose a "Buffered Saline"

The Examiner rejected claims 1-8, 12-21 and 25-28 under 35 U.S.C. 102(b) as allegedly anticipated by Schantz *et al.* (EP 0 593 176 A2). Applicants respectfully traverse this rejection.

The Examiner alleges that Schantz *et al.* disclosed a pharmaceutical composition comprising crystalline botulinum toxin type A in buffers of about pH 5, pH 5.5. and pH 6.2.

Applicants first respectfully point out to the Examiner that a pH of 6.2 is not within the "between pH 5 and 6" limitation of the amended claims. Therefore, the Schantz *et al.* pH 6.2 formulation does not anticipate the instant claims.

In regards to the pH 5.0 and pH 5.5 botulinum toxin formulations, Applicants respectfully point out to the Examiner that these formulations do not contain a "buffered saline" as recited by the instant claims. On the contrary, the Schantz reference teaches away from the use of a buffered saline by specifically requiring the disclosed liquid botulinum toxin formulations compositions to be "sodium chloride free." *See, e.g.*, Abstract; pg. 2, lines 44-46; claim 1. The Schantz reference specifically teaches that "[t]he most critical factor was the absence of sodium chloride in the solution." *See* pg. 4, lines 1-2. Moreover, comparing all experimental conditions used in the Schantz reference, no experiment was conducted using the combination of a solution with a pH between pH 5 and pH 6 **and** saline. *See* Table 1 at pg. 5.

Therefore, because the Schantz reference fails to disclose the use of a buffered saline at the recited pH ranges claimed, it does not anticipate the instant claims. Applicants respectfully request that the Examiner withdraw this rejection.

VI. Rejections Under 35 U.S.C. § 103

A. The Combination of Schwarz or Saprykina or Sacks and Schantz *et al.* Fails to Meet the Prima Facie Requirements for Obviousness

The Examiner has rejected claims 14, 15, 27 and 28 under 35 U.S.C. §103(a) as being allegedly unpatentable over Schwarz, or Saprykina or Sacks as applied to claim 1 or claim 16 and further in view of Schantz *et al.* Applicants respectfully traverse this rejection.

In order to establish a prima facie case of obviousness, the Examiner must satisfy three basic criteria: 1) there must be some suggestion or motivation to modify or combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references combined must teach or suggest all of the claim limitations. As detailed above, the Schwarz, Saprykina, Sacks and Schantz references, even when combined, do not teach or suggest all of the limitations in the instant claims. For example, the references combined do not teach the limitation of a "buffered saline" solution as recited in claims 1 and 16, from which claims 14, 15, 27 and 28 depend thereto.

Moreover, the references when combined actually teach against the instant claims. In particular, Schantz *et al.*, as mentioned above, teaches against the use of a buffered saline by specifically requiring the compositions to be "sodium chloride free." *See, e.g.*, Abstract; pg. 2, lines 44-46; claim 1. The Schantz reference specifically teaches that "[t]he most critical factor was the absence of sodium chloride in the solution." *See* pg. 4, lines 1-2. Therefore, one of ordinary skill in the art would not have any motivation or suggestion to combine the references, nor would they have any reasonable expectation of success if the teachings of the references are combined because Schantz *et al.* specifically teaches that a liquid botulinum toxin formulation containing saline would fail. The combination of Schwarz, Saprykina or Sacks together with Schantz *et al.* teaches away from the instant claims.

For the reasons above, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness. Applicants hereby request that the Examiner withdraw this rejection.

B. The Combination of Schwarz or Saprykina and Melling *et al.* Fails to Meet the Prima Facie Requirements for Obviousness

The Examiner has rejected claims 9-11 and 22-24 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schwarz or Saprykina *et al.* as applied to claim 8 or claim 21, and further in view of Melling *et al.* (Eye 2:16-23 (1988)). Applicants respectfully traverse this rejection.

As detailed above, the Schwarz or Saprykina references do not teach or suggest all of the claim limitations in the instant claims. For example, the references do not teach the limitation of a "buffered saline" solution as recited in claims 1 and 16, from which claims 9-11 and 22-24 depend thereto. Adding the Melling *et al.* reference does not cure this deficiency. Melling *et al.* does not disclose the use of a "liquid pharmaceutical botulinum toxin formulation" containing a "buffered saline capable of providing a buffered pH range between pH 5 and pH 6." Because the combination of Schwarz or Saprykina and Melling *et al.* do not teach or suggest all of the limitations in the instant claims, the references do not render the instant claims obvious.

Moreover, the references when combined teach away from the instant claims. In particular, Melling *et al.* teaches the use of freeze drying the botulinum toxin solution in a "diluent containing lactose and human serum albumin." *See* pg. 20, 2nd col., 2nd full paragraph. The Melling reference does not teach the use of an acidic buffer "between pH 5 and pH 6", as recited in the instant claims. The Melling reference also does not teach the use of a "buffered saline" solution, again as recited in the instant claims. Therefore, one of ordinary skill in the art would not have any motivation or suggestion to combine the references, nor would they have any reasonable expectation of success if the teachings of the references are combined because the combination of the references are silent regarding the use of these limitations. The combination of Schwarz or Saprykina together with Melling *et al.* teaches away from the instant claims.

For the reasons above, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness. Applicants hereby request that the Examiner withdraw this rejection.

C. The Sacks Reference Fails to Meet A Prima Facie Requirement for Obviousness

The Examiner has rejected claims 12, 13, 25 and 26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sacks *et al.* as applied to claim 8 or claim 21 above.

As detailed above, the Sacks reference does not teach or suggest all of the limitations in the instant claims. For example, Sacks fails to teach the limitation of a "buffered saline" solution as recited in claims 1 and 16, from which claims 12, 13, 25 and 26 depend thereto. In addition, one of ordinary skill in the art would not look to the Sacks *et al.* reference because it teaches away from the instant claims, *i.e.* it teaches a botulinum toxin at pH 6.0 that is ***not*** stable. Sacks *et al.* notes that the liquid formulation stored in pH 6.0 phosphate buffer for 1 year at 4:0 °C "lost more than 60% of its original lethality." One of ordinary skill in the art, with guidance from the specification, would know that a loss of 60% of the original lethality is not a stable formulation. In fact, this amount is equivalent to the large losses found in prior art formulations, where losses of 44% and 70% of potency were reported in reconstituted botulinum toxin A formulations. *See* pg. 2-3 of the instant application. Therefore, one of ordinary skill in the art in looking at the Sacks reference would know that it teaches away from the instant claims, *i.e.* it does not teach a "stable liquid pharmaceutical botulinum toxin formulation comprising buffered saline capable of providing a buffered pH range between pH 5 and pH 6."

Because the Sacks reference does not teach or suggest all of the claim limitations, and it teaches away from the instant claims, it cannot render claims 12, 13, 25 and 26 obvious. Applicants hereby request that the Examiner withdraw this rejection.

CONCLUSION

In summary, Applicants submit that the references cited by the Examiner do not anticipate or render obvious the instant claims. Particularly, the references, either alone or in combination, fail to disclose:

- A stabilized pharmaceutical liquid botulinum toxin formulation comprising:
- A therapeutic concentration suitable for use in humans of purified botulinum toxin
- Buffered saline between pH 5 and pH 6
- Which is capable of being stable for at least a year between 0 and 10 degrees centigrade, +/- 10%, or for at least 6 months between 10 and 30 degrees centigrade, +/- 10%.

In light of the remarks set forth herein, Applicants believe that they are entitled to a letters patent. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Please charge any fee due in connection with this submission to Deposit Account No. 23-2415. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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